Ericson[2] reported two cases of myopia during pregnancy. One patient was a 24-year-old woman in whom myopia developed six hours after she took one tablet of Hygroton. This was corrected by —3.00 D sphere in the right eye and —2.50 D sphere in the left eye. Bilateral macular edema was also noted. Use of the drug was stopped and vision was normal two days later. When the drug was given again, three months after parturition, no eye symptoms occurred. In the second case, that of a 28-year-old woman, myopia of —4.25 D in the right eye and —4.50 D in the left eye developed eight hours after ingestion of one tablet of Hygroton. No retinal edema was present. The patient took no more of the drug and vision was normal three days later. A few weeks later, while the patient was still pregnant, two tablets of Hygroton in divided doses produced myopia of —1.50 D in each eye. This cleared in three days after cessation of therapy.

Pallin and Ericson[3] did ultrasound determinations on a 45-year-old policeman who noted poor vision seven hours after taking a second tablet of Hygroton. A week earlier he had experienced severe nausea, vomiting and diarrhea five hours after one tablet of Hygroton but his vision had not been impaired at that time. The second episode was also accompanied by similar gastrointestinal disturbances in addition to poor vision and a pruritic rash. The gastrointestinal symptoms and rash cleared in 24 hours. Two days after the second Hygroton tablet was ingested the visual acuity was correctable to 20/20 with a —2.50 D sphere in each eye. The next day, after discontinuance of the drug, eye findings were the same. Ultrasound studies, one done at that time and another three weeks later, showed that the lens thickness was greater during the myopic phase.

The mechanism for the transient myopia produced by Hygroton, a heterocyclic sulfonamide, is unknown. Pallin and Ericson[3] expressed belief that certain features of the case they reported pointed to an allergic reaction. In the case reported herein, the periorbital edema, chemosis and conjunctivitis can also be interpreted as being consistent with allergic reaction. Mattson[4] explained the transient myopia occurring with sulphonamide drugs as due to an allergic edema of the ciliary body. This edema would produce myopia by relaxing the lens zonules. Swelling of the eyelids,[5] chemosis[5] and conjunctivitis[6] have also been associated with use of other sulfa drugs. Ericson[2] thought the myopia could be the result of a change in the salt and water content of the lens, and that pregnant patients are more susceptible to the change.

Other drugs which have been reported to produce transient myopia include neoarsphenamine,[7] acetazolamide (Diamox),[8] hydrochlorthiazide (Hydro-Diuril),[9] and tetracyclines.[10]

The signs and symptoms caused by Hygroton, although alarming, disappear completely following discontinuance of the drug.

Summary

A 36-year-old woman had conjunctivitis, chemosis, periorbital edema and myopia following ingestion of three tablets of Hygroton (50 mg). These signs disappeared within one week following discontinuance of the drug.

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Hepatitis and Aplastic Anemia

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WHILE HEPATITIS is occasionally complicated by hematological problems, for the most part these problems are of no great moment. They may consist of hemolytic anemia, leukopenia and thrombocytopenia. Usually recovery occurs spontaneously as hepatitis abates. In the past several years there has been an occasional report of a much more serious complication, that of aplastic anemia following hepatitis. Most of the reports have been in the European literature, with only a few in this country. The purpose of this paper is to report an incident of hepatitis followed by a fatal course of aplastic anemia.

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Report of a Case

An 18-year-old male Caucasian was admitted to Parkwood Community Hospital on 8 May 1967 with chief complaint of fatigue, lethargy, anorexia and nausea. He had been well until, a week before admission, he began to experience fatigue and headaches. A physician who examined him at that time noted enlarged cervical lymph nodes and weakness. The patient had noted neither purpura nor easy bruising. He complained of some irritation of the throat but blood cell counts and heterophil titers were within normal limits.

The patient had been completely well until the onset of these symptoms, except for a traumatic accident to his teeth several weeks before they began. He had not taken any drugs before the onset of symptoms and, so far as he knew, he had not been exposed to any noxious substances or radiation. There had been no loss of weight and no history of pruritus but the patient had noted darkening of the urine. During the week before admission he had been given penicillin and the pharyngitis seemed to improve, although fatigue and weakness continued. By the time he was admitted to the hospital, most of the lymph node enlargement had receded and appetite had improved somewhat. On questioning, the patient said he had not had dysuria, urinary frequency, joint pain or chest pain.

At the time of admission to hospital, vital signs were normal and the patient appeared not to be in distress. There was questionable icterus of the conjunctivae. Neither ecchymosis nor purpura was present but there was a mild pustule-like rash over the hands which was non-pruritic and non-erythemic. The lungs were clear to auscultation and percussion, no cardiac murmurs were heard and the heart appeared to be of normal size. The edge of the liver was palpated 1 cm below the right costal margin and was slightly tender. The spleen was not palpable. The abdomen was not distended and no abnormality of bowel sounds was noted. Preceding and during his entire hospital stay the patient remained afebrile.

The hemoglobin on admission was 15 gm per 100 ml and the hematocrit was 47. Leukocyte numbered 4,900 per cu mm with 65 percent neutrophils, 28 percent lymphocytes, 5 percent monocytes and 2 percent eosinophils. Platelets appeared normal on the smear. Some of the lymphocytes showed atypical changes. Anti-streptolysin O (ASO) titer was 125 units. Prothrombin time was 15 seconds (control 14 seconds). Results of urinalysis and C reactive protein determination were within normal limits. Alkaline phosphatase was 4.0 units (normal 1 to 3.5). Alpha hemolytic streptococcus grew on a culture of material from the throat. The total bilirubin was 4.6 mg per 100 ml, direct 2.4 mg and indirect 2.2 mg. Serum glutamic pyruvic transaminase (SGPT) was 860 units, serum glutamic oxalacetic transaminase (SGOT) 100 units and lactic dehydrogenase (LDH) 790 units. Total serum protein was 6.7 gm per 100 ml with an albumin-globulin ratio of 4.0 to 2.7. The heterophil was negative. Creatinine content was 1.1 mg per 100 ml. Two-hour post-prandial blood sugar was 110 mg per 100 ml and blood urea nitrogen (BUN) 10 mg per 100 ml. Urobilinogen content of a 24-hour specimen of urine was 6.3 mg per 100 ml (normal 0-4 mg).

On 11 May 1967, three days after the patient was admitted, hemoglobin was 16.3 gm per 100 ml, the hematocrit 50 and leukocytes 4,400 per cu mm, with 11 percent banded and 35 percent segmented forms, 47 percent lymphocytes, 1 percent monocytes, 3 percent eosinophils and 3 percent basophils. Ten percent of the lymphocytes were atypical. Total bilirubin was 3.2 mg per 100 ml, with direct 1.2 and indirect 2.0 mg. SGPT was 950 units. An x-ray film of the chest was within normal limits.

The patient continued to do well and he was sent home for further care. On 18 May 1967, total bilirubin was 1.0 mg per 100 ml, with direct of 0.3 and indirect of 0.7 mg, and SGPT was 400 units. Five days later total bilirubin was 1.8 with a direct of 0.4 and indirect of 1.4 mg, and SGPT was 310 units. The patient continued to do well. His appetite increased, he was no longer weak and he was able to carry on normal functions.

On 1 June 1967 the patient was relatively asymptomatic. Hemoglobin was 14.2 gm per 100 ml, and hematocrit 44. Leukocytes numbered 4,800 per cu mm, with 4 percent banded, 60 percent neutrophils, 35 percent lymphocytes and 1 percent monocytes. Total bilirubin was 1.9 mg per 100 ml, with direct of 0.4 and indirect of 1.5. SGPT was 102 units.

On 8 June 1967 the patient began to notice a petechial rash on the wrists, hands and ankles. He had a low grade fever and began to feel somewhat weak. The rash persisted and more petechia and ecchymosis began to appear. On 13 June 1967, the patient was readmitted to the hospital. At examination he appeared well-developed and well-

nourished. Vital signs were normal. The conjunctiva appeared somewhat icteric and pale. There were ecchymotic and petechial areas on the soft and hard palate and multiple areas of ecchymosis on oral mucosa and lips. On examination of the gums gingival hyperplasia, tenderness to palpation and easy bruising were noted. A fundoscopic examination revealed no hemorrhages or exudates. The lungs were clear to auscultation and percussion. Multiple petechiae were noted at the ankles and on the upper dorsum of the feet. There appeared to be resolving ecchymotic areas of the lumbosacral area, and the anterior tibial area showed signs of recent bruising and ecchymosis. The spleen and liver were not palpable. The remainder of the physical examination was within normal limits.

Hemoglobin was 11.2 gm per 100 ml and the hematocrit was 30. Leukocytes numbered 1,000 per cu mm with 66 percent lymphocytes and 34 percent segmented forms. There were 50,000 platelets per cu mm and there were no reticulocytes. SGPT was 15 units and the alkaline phosphatase was within normal limits. Total bilirubin was 3.1 mg per 100 ml, with direct 0.1 mg and indirect 3.0 mg. Total protein, albumin-globulin ratio and thymol turbidity were all within normal limits. Partial thromboplastin time was 89 seconds (normal 70 to 150) and prothrombin time 14 seconds (control 14 seconds). Results of direct and indirect Coombs' tests were negative. LDH was 240 units and BUN was 12 mg per 100 ml. Uric acid was 7 mg per 100 ml. Results of urinalysis were within normal limits.

The patient was afebrile and remained so during the hospital stay. Bone marrow aspiration was attempted but no material was withdrawn. A Vim-Silverman biopsy of the marrow was then performed and pronounced hypoplasia, with very few marrow elements present, was noted (Figure 1). No criteria of leukemia were present. On 14 June 1967, serum iron was 85 mg per 100 ml (normal 65 to 150) and iron-binding capacity was 420 mg per 100 ml (normal 255 to 419). Total bilirubin was 3.8 mg per 100 ml with direct of 1.3 mg and indirect of 2.5 mg. Culture of material from the throat grew hemolytic staphylococcus aureus. There was no growth on cultures of blood.

Antibiotic therapy was begun. On 15 June 1967, hemoglobin was 9.2 gm per 100 ml, hematocrit 26, and leukocytes 800 per cu mm with 4 percent band forms, 4 percent neutrophiles, 89 percent lymphocytes and 3 percent eosinophils. There were 30,000 platelets per cu mm. Haptoglobins were 37 mg per 100 ml (normal 40 to 170). Serum protein electrophoresis revealed a total protein of 7.5 gm per 100 ml, with albumin 5.3, globulins 2.2, alpha 1 globulins 3.6 percent, alpha 2 globulins 7.5 percent, beta globulins 6.5 percent of the total and gamma globulins 10 percent of total (normal 9 to 22). Steroids were added to the regimen and the patient remained afebrile and in no apparent distress.

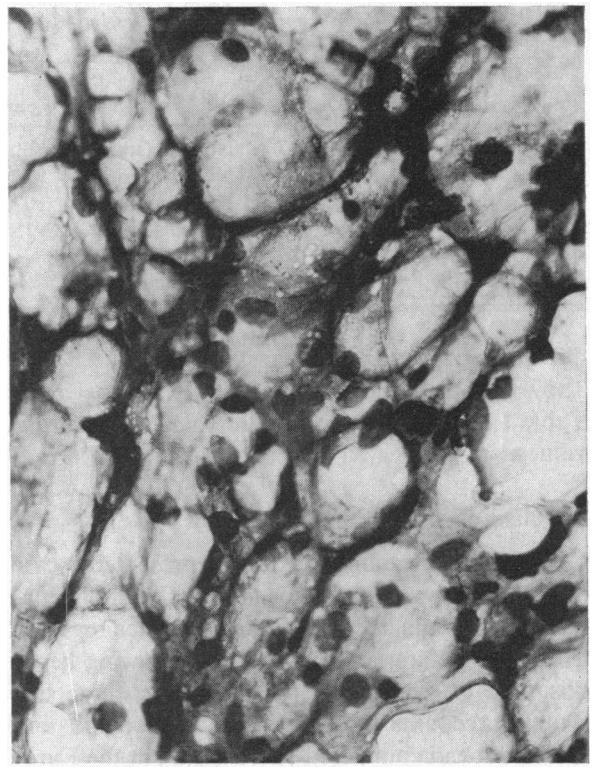

Figure 1.—Section of bone marrow showing absence of myeloid and eythroid elements (× 500).

On 16 June 1967, the patient was transferred to UCLA Medical Center for further care. There infusions of fresh platelets and whole blood were given, and testosterone and steroid therapy were begun. Bone marrow studies still showed pronounced hypoplasia and the clinical status of the patient did not improve. He remained afebrile. Antibiotic therapy for the throat infections was continued, and as before blood cultures continued to show no growth of organisms.

The patient was discharged from hospital 23 June 1967, to be followed as an outpatient. Forty-eight hours later he was readmitted with a high fever and with increased bleeding tendencies and multiple bruises. The clinical course from then on was one of continued deterioration, despite the use of high doses of steroids, antibiotics, testosterone

TABLE 1.—*Hematologic and Enzyme Values in a Case of Hepatitis and Aplastic Anemia*

Date	Hemaglobin (gm per 100 ml)	Leukocytes (per cu mm)	Hematocrit	Platelets	SGPT
5- 8	15.9	4,900	47	Normal (smear)	860
5-11	16.3	4,400	50	Normal (smear)	950
6- 1	14.2	4,800	41	Normal (smear)	102
6-13	11.2	1,000	30	50,000 cu mm	15
6-15	9.2	800	26	30,000 cu mm	—
7-11	—	600	22	2,000 cu mm	—

and platelet and blood transfusions. On 18 July 1967 the patient died. Autopsy was not done. Table 1 summarizes the hematological and enzyme values.

Discussion

In 1962 Deller and coworkers[1] presented a case of fatal pancytopenia associated with viral hepatitis. Three years later Levy and associates reported five cases of fatal aplastic anemia following hepatitis.[2] Up to the time of the reports by these two groups, accounts of cases of pancytopenia and aplastic anemia appeared sporadically in the European literature. Lorenz and Quaiser[3] and later Kosan[4] reported cases which are almost identical to those cases reported in American journals.[1,2,5] Rubin and coworkers[6] recently presented ten cases and reports have appeared from time to time in the British medical journals.[7] The clinical course and progress in all the cases reported, including the one herein, seem to point to more than a coincidental association between hepatitis and aplastic anemia. The temporal and clinical relationships in the present case closely resemble those noted in other cases, especially those of Rubin.[6] In most cases the hepatitis is resolved, both clinically and cytologically, by the time pancytopenia develops. Most patients are males and most die.

It is well known, of course, that the hemolytic anemia of thrombocytopenia purpura of leukopenia are all hematological complications of hepatitis. However, pancytopenia with severe aplastic anemia seems to be a rather unusual occurrence.

If a causal association does exist, how can the mechanism of this hematological catastrophe be best explained? Is the virus that causes the hepatitis an agent which can cause severe hematological damage? Or does the hepatitis itself produce some metabolic product which damages the bone marrow? It would appear that the latter question is less to the point than the former, since hepatic function usually is adequate by the time pancytopenia develops.

It is known that viral infections may depress one or all three elements of the peripheral blood. Hammon and Enders[8] showed that the virus of malignant leukopenia caused bone marrow aplasia in cats. In addition, Lawrence's[9] work also revealed that pronounced agranulocytosis may occur from viral infection. Evidence indicating that viruses containing ribonucleic acid may cause pancytopenia was observed in cases of Dengue fever.[10] However, hepatitis has not been noted to be a clinical concomitant in these cases. In addition, temporary pancytopenia has been reported in cases of congenital rubella syndrome, and myxoviruses have been associated clinically with leukopenia or thrombocytopenia.

Since the virus of infectious hepatitis is pantropic,[11] it is possible that the aplastic anemia seen in these cases is the ultimate expression of the leukopenia that is so commonly found in cases of infectious hepatitis.

This association of hepatitis and aplastic anemia may explain some of the cases of idiopathic aplastic anemia, since many of them may have been preceded by unrecognized or subclinical cases of hepatitis.

Summary

A case of fatal aplastic anemia following an episode of hepatitis is presented. The temporal and spatial relationships of this case follow closely the cases previously reported.

The case is presented as another documentation of two diseases which may be related by more than coincidence.

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